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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/510,562	02/22/2000	Gerard Housey	395/35	3061

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EXAMINER	
GUZO, DAVID	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/510,562	HOUSEY, GERARD	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33,34,36,37,43-50,59-65,71-78 and 87-128* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33,34,36,37,43-50,59-65,71-78 and 87-128* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Applicant, in the amendment filed 4/11/06, added new claims 121-128 which recite a method for determining "whether a chemical agent is a **specific inhibitor or activator** (emphasis added) of an enzyme in a cell". The Courts have previously addressed the issue of the meaning of the terms "specific" or "specifically" with regard to the nature of the binding of the candidate agent to the protein of interest (POI). The following is an analysis of the CAFC's ruling concerning said language.

Claim interpretation and Decision in *Housey Pharmaceuticals Inc. v. AstraZeneca UK Ltd.*, 70 USPQ2d 1641 (CAFC 2004)

In the decision in Housey Pharmaceuticals Inc. v. AstraZeneca UK Ltd., 70 USPQ2d 1641 (CAFC 2004), the court ruled that the claim language "inhibitor or activator" of a protein of interest (POI) was not limited to substances which directly bind to the POI. Specifically (p. 1641) the court ruled that:

Claimed method of determining whether particular substance, such as candidate for pharmaceutical product or drug, is "an inhibitor or activator of a protein" of interest is properly construed to encompass substances that inhibit or activate biological activity of protein of interest in cell without binding to POI itself, since claim language indicates that substance is "inhibitor or activator" of protein if it yields positive response to claimed method, since specification likewise defines "inhibitors"and "activators" in terms of biological activity of POI without reference to binding, since dictionary definitions do not compel inclusion of direct-binding concept as limitation on claimed method, and since intrinsic evidence does not clearly disavow this broad plain meaning, and instead affirmatively demonstrates that inventor intended broader meaning that is not limited to direct binding; neither "of a protein" claim language, nor recurring presence of "specific" and "specifically" in specification and prosecution history, warrants contrary conclusion (emphasis added).

Furthermore, with regard to use of the terms "specifically" and "specific" to define the inhibitor or activators of the POI, the court (p. 1646) noted that:

Similarly, Housey argues that the recurring presence of the terms "specific" and "specifically" in the specification and the prosecution history conclusively demonstrates that the inhibitor or activator operates by binding with the POI. See, e.g., '281 patent, col. 1, ll. 10-12 ("In particular, [the invention] is concerned with a method of screening for substances which specifically inhibit or activate a particular protein." (emphasis added)); id. at col. 2, ll. 27-28 (describing the invention as having a "specificity for detecting an active agent exceeding that of" the prior art assays); id. at ll. 28-32 ("[T]he method which we describe herein involves the generation of a cell line purposefully engineered to detect both stimulatory and inhibitory agents which are absolutely specific for any given protein which affects the cultural of morphological characteristics of a cell." (emphasis added)); id. at col. 9, ll. 30-31 (stating that the method was screening for "substances which may contain biologically active agents specific to the POI" (emphasis added)). Leaving aside the absence of the word "specific" in the claim language (and our repeated warnings not to import limitations from the specification that are not present in the claims, Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1325 [65 USPQ2d 1385] (Fed. Cir. 2003) ("The danger of improperly importing a limitation is even greater when the purported limitation is based upon a term not appearing in the claim.")), this language from the specification does not lead to a strong inference of direct binding to the POI. As the above-quoted sections of the prosecution history demonstrate, the use of "specific" suggests equally as strongly that the biological activity of the POI is affected, through a direct or indirect mechanism, when the biological activity of other proteins in other biochemical pathways is not. Furthermore, the specification, too, equates specificity with the biological effect of the inhibitor or activator, not with any particular mechanism of action.

Since Housey stipulated that if the claim construction was not limited to inhibitors or activators which directly bound to the POI, its patents would be invalid and not infringed, the decision of the CAFC which found in favor of defendants (p. 1641) is final:

Housey Pharmaceuticals, Inc. ("Housey") sued AstraZeneca UK Ltd., AstraZeneca LP, AstraZeneca Pharmaceuticals LP, Aventis Pharmaceuticals, Inc., Bristol-Meyers Squibb Co., Merck & Co., Inc., Roche Holdings, Inc., Hoffman-La Roche Inc., Roche Laboratories, Inc., Syntex (U.S.A.) Inc., Wyeth, and Wyeth Pharmaceuticals, Inc. (collectively "defendants") in the United States District Court for the District of Delaware, alleging infringement of four patents addressing methods of screening for protein inhibitors and activators. The district court construed several of the limitations of the patent claims, including "inhibitor or activator of a protein." Bayer AG v. Housey

Pharm., Inc.,1 No. 01-148-SLR (D. Del. Nov. 12, 2002). Housey subsequently stipulated that, if this construction were not reversed or modified on appeal, its patents would be invalid and not infringed. Housey Pharm., Inc. v. Abbott Pharm., Inc., No. 01-401-SLR (D. Del. Nov. 26, 2002). The district court ordered a final judgment of invalidity and noninfringement. Housey Pharm., Inc. v. Abbott Pharm., Inc., No. 01-401-SLR (D. Del. Nov. 27, 2002). We conclude that the district court's construction of "inhibitor or activator of a protein" was not erroneous, and we therefore affirm the judgment.

In the instant case (Serial No. 09/510,562), applicant claims essentially the same subject matter as recited in the patents which have been invalidated with the exception of including the term "specific inhibitor or specific activator" of a POI in the claims. However, as noted by the CAFC, this terminology would not serve to limit the claimed subject matter to substances which directly bind to the POI, but instead, the prosecution history of the parent cases indicates that the instant claims read on methods of determining whether a substance inhibits or activates the biological activity of the POI by direct or indirect means. The instant claims 121-128 will be interpreted in light of the CAFC ruling.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-34, 36-37, 43-50, 59-65, 71-78, 87-120 and 125-128 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is maintained for reasons of record in the previous Office Action (mailed 10/5/05) and for reasons outlined below. Claims 125-128 are added to this rejection as a result of applicant's amendment filed 4/11/06.

Applicant traverses this rejection by pointing out the significance of the concept of the responsive phenotypic change and graded cellular response to the claimed invention. With regard to the examiner's interpretation of the amended claim language, applicant indicates that:

> Nevertheless, it appears that the Examiner now correctly states what is meant to be claimed when he observes that "the claims appear to require that the level of the enzyme be maintained before the inhibitor is added, during the period the inhibitor is present, and after the inhibitor is removed.

Also, contrary to the Examiner's assertion of new matter, applicant indicates that the specification discloses an example which provides test cells in which the level of PKC is maintained when in contact with an inhibitor or activator.

Applicant's arguments filed 4/11/06 have been fully considered but they are not persuasive. There is no support in the specification for limitations concerning the level of the target enzyme in the cell when in contact with the potential inhibitor or activator. The instant claims, as currently drafted, would **specifically exclude** circumstances wherein the target enzyme is irreversibly bound to the potential inhibitor and/or is destroyed and hence the level of said enzyme cannot be **maintained** such that the cell remains capable of exhibiting the phenotypic response to the potential inhibitor. The

specification does not provide support for this limitation. Indeed, the specification provides no procedure(s) for determining the level of the target enzyme in the presence of a potential inhibitor or activator. With regard to applicant's assertion that the example in the specification dealing with TPA provides support for the claimed invention, it is noted that one example involving the growth and morphological responses to TPA in cells over-expressing PKC does not provide support for the broad limitation recited in the claims.

With regard to new claims 125-128, applicant recites the limitation that the "level of the enzyme is not down-regulated in the presence of a specific inhibitor or activator of the enzyme". These claims are also rejected as containing impermissible new matter because the claims would **specifically exclude** circumstances wherein the target enzyme is irreversibly bound to the potential inhibitor and/or is destroyed and hence the level of said enzyme cannot be **maintained** in the presence of the inhibitor but is present before the inhibitor is added and after the inhibitor is withdrawn such that the cell remains capable of exhibiting the phenotypic response to the potential inhibitor. The specification does not provide support for this limitation.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 121-124 are rejected under 35 U.S.C. 102(b) as being anticipated by Drebin et al.

This rejection is applied as a result of applicant's amendment filed 4/11/06. It is noted that the rejection of claims 33-34, 36, 43-44, 46-47, 49, 63-64, 71-72, 74-75,77,88,90-92,94-95,97-98,100,106-017, 109-110, 112-113, 115 and 118 over Drebin et al. made in the previous Office Action is withdrawn as a result of applicant's arguments. Applicant's arguments are not germane to the instant claims as the instant claims do not recite the same limitations as those previously rejected over Drebin et al.

Applicants and Drebin et al. (Cited by applicants, Cell, Vol. 41, 1985, pp. 695-705, see whole article, particularly the results section on pp. 696-698 and pp. 700-701) both recite the same method whereby a specific chemical inhibitor of a target enzyme is identified. Drebin et al. recite a method comprising determining whether a chemical agent (i.e. an antibody) specifically interacts with a protein or enzyme (i.e. *neu*-oncogene product, p185, expressed by a vector transfected into the cell) in a cell wherein expression of the p185 protein in the cell evokes a responsive change (i.e. a graded response) in a phenotypic characteristic of the cell (anchorage independent growth) other then the level of the enzyme in the cell by providing a first mammalian cell which overproduces the protein or enzyme and exhibits said phenotypic response to the enzyme and a second mammalian cell which produces the protein or enzyme at a lower level or not at all compared with the first cell line, incubating the chemical agent with both cell lines and comparing the phenotypic response of the cell lines to determine if the agent is an inhibitor of the protein or enzyme. The antibodies disclosed by Drebin et

al. are contemplated for use in contacting cells expressing oncogene products and for use in treating malignancies. Drebin et al. therefore teaches the claimed invention.

Claims 121-124 are rejected under 35 U.S.C. 102(b) as being anticipated by Hsiao et al.

Both applicant and Hsiao et al. (Mol. Cell. Biol., 1986, Vol. 6, No. 6, pp. 1943-1950, see whole article, particularly the Abstract; Table 1; pp. 1944-1946, 1950) recite a method for inhibiting a particular protein of interest (POI, i.e. an enzyme such as activated human bladder c-Ha-ras oncogene, associated with increased tumorgenesis) in a cell (which does not produce the POI prior to introduction of the POI into the cell) comprising determining whether a substance (i.e. tumor promoters TPA or teleocidin) specifically interacts (directly or indirectly) with a POI whose production in a cell evokes a responsive change (i.e. a graded response) in a phenotypic characteristic of the cell, other than the level of the POI, by providing a first mammalian cell which overproduces the POI and exhibits said phenotypic response to the POI (i.e. foci formation in cell culture) and a second mammalian cell which produces the POI at a lower level or not at all compared with the first cell line, incubating the substance with both cells lines and comparing the phenotypic response of the cell lines to determine if the substance is an inhibitor of the POI. The gene encoding activated human bladder c-Ha-ras oncogene is under control of a promoter operable in the cell wherein expression of said oncogene results in a responsive change in the host cells as a result of phosphorylation of a

substrate such as Raf in the signal pathways involved in oncogenesis. Hsiao et al. therefore teaches the claimed invention.

Claims 121-124 are rejected under 35 U.S.C. 102(b) as being anticipated by Hapel et al.

Applicant's invention is as described above.

Hapel et al. (Lymphokine Res., 1986, Vol. 5, No. 4, pp. 249-254, see whole article, particularly the Abstract, pp. 250, 252) recite a method which provides a first cell line (FDC-P1-IL3) which produces the POI (IL-3) wherein said POI is introduced into the parent cell line (FDC-P1) by a retroviral vector and wherein production of the POI causes the cells to become leukemogenic (phenotypic characteristic) and provides a second cell line (FDC-P1) which does not produce IL-3, incubating both cells in the presence of an anti-ILK-3 antibody (putative inhibitor) and comparing the responsive changes of the first cell to the responsive change of the second cell and examining the treated first cell to determine whether the responsive change is a phenotypic characteristic which is increased or decreased in response to the substance. Hapel et al. found that the inhibitor (antibody) completely eliminated growth of the FDC-P1-IL3 cells while growth of FDC-P1 cells was not as severely limited (at the same antibody concentrations). Hapel et al. therefore teaches the claimed invention.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 121-124 are rejected under 35 U.S.C. 102(a) as being anticipated by Riedel et al.

Applicant claims methods for determining whether a substance is a specific inhibitor or activator of a POI (enzyme) in a cell where expression of the POI results in a phenotypic characteristic in the cell, said method comprising providing a test mammalian cell line which produces said POI and exhibits a phenotypic response (which can be a graded cellular response) to the POI, providing a second mammalian cell line which is alike to the first cell line but which produces the POI at lower levels or not at all, incubating the test substance with the first and second cell lines and comparing the phenotypic responses of the first and second cell lines to the test chemical.

Riedel et al. (cited by applicants, Science, Vol. 236, April 1987, pp. 197-200, see entire article, particularly the Abstract', Fig. 2-3., p. 198, last paragraph; p. 199, 3rd and 4th paragraphs bridging the 2nd and 3rd columns) recites a method for determining whether an agent (epidermal growth factor, EGF) can activate or inhibit an enzyme (chimeric human epidermal growth factor (EGF) - avian *erb*B oncogene product, HER-*erb*B) expressed in a test mammalian cell. Expression of the HER-*erb*B gene product (as a result of transformation of test cells with a vector encoding the HER- *erb*B gene product, wherein said HER-*erb*B gene is under control of a promoter) causes a phenotypic change (graded cellular response) in the cells (cells are transformed, ability

to grow in soft agar in the absence of EGF). The agent EGF is incubated with the test cells and a control cell which does not produce the enzyme (containing the vector but without the sequence encoding the HER-*erb*B protein), the phenotypic responses (changes in cellular transformation, foci formation) of the two cells are compared and a binding assay is used to determine that the chimeric enzyme directly binds EGF. EGF is also used to treat the test cell to determine whether it exhibits a change in a graded cellular response (transformation response of cells in culture). EGF can be an activator of the HER-*erb*B enzyme under some circumstances (p. 199, top right column) and can be an inhibitor (p. 199, 3rd paragraph, left column) under other circumstances. The responsive change in a phenotype includes phosphorylation of an intracellular protein substrate of the enzyme. Riedel et al. therefore teaches the claimed invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-34, 36-37, 43-50, 59-65, 71-78 and 87-120 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is maintained for reasons of record in the previous Office Action and for reasons outlined below.

Applicant traverses this rejection by argument and by supplying a 37 CFR 1.132 Declaration by Dr. James D. Griffin (Griffin Declaration). Applicant and Declarant argue that the stable overproduction of the target enzyme is a way to evoke the phenotypic response that is capable of distinguishing between chemical inhibitors or activators of the target enzyme as opposed to agent which affect other proteins or non-protein targets in the cell. Applicant and declarant argue that prior art methods employing phenotypes to identify active substances were not specific with respect to any cellular component and that applicant's method employing a graded cellular response provides this specificity. With regard to the examiner's citation of the Hsiao et al. reference, applicant and declarant argue that Hsiao et al. does not use a graded cellular response or any other responsive change in a phenotypic characteristic and Hsiao's method does not rely on any association between POI levels and phenotype that would enable one of skill in the art predictably identify compounds that directly activate or inhibit $p21^{ras}$. With regard to the examiner's citation of the Ledwith et al. reference, applicant and declarant also argue that Ledwith et al. does not use a graded cellular response or any other responsive change in a phenotypic characteristic and that Ledwith et al. only established a relationship between a protein in a cell that is not the POI and the level of a compound that reduces the amount of that protein.

Applicant also argues that the specification provides working examples to demonstrate that chemical agents that directly modulate a POI cause changes in a specialized phenotype that is observable when the POI is over-expressed. Applicant

asserts that using the instant invention, he was able to identify tamoxifen as a direct inhibitor of protein kinase C.

Wirth regard to the decision of the Technical Board of Appeal of the EPO in case T 0729/00 3.3.4, applicant notes, the decision of the Opposition Division of the European Patent Office which was the basis for the appeal was unanimously in favor of the Patentee, that the claims before the Technical Board of Appeal were not the instant claims, and that the decision of the Technical Board of Appeal is not binding on the Patent Office.

Applicant's arguments have been fully considered but they are not persuasive. Also, the Declaration under 37 CFR 1.132 filed 4/11/06 is insufficient to overcome the rejection of claims 33-34, 36-37, 43-50, 59-65, 71-78 and 87-120 based upon 35 USC 112, 1st paragraph as set forth in the last Office action because of the following reasons. Initially, the examiner notes the meaning given to the terms "phenotypic response" or "responsive change in a phenotypic characteristic" by the District Court in the Markman hearing in *Bayer AG v. Housey Pharm., Inc.* (D. Del. Nov. 12, 2002). These terms were defined as:

> The term "phenotypic response" or "responsive change in a phenotypic characteristic" shall be construed to mean the characteristic which is changing and which the person skilled in the art is measuring, which is reflective of the activation or inhibition of the protein of interest.

Hence the phenotypic response can be any change in any phenotypic characteristic which is reflective of the activation or inhibition of the POI. The over-production of the POI as a way to evoke the phenotypic characteristic (which results from the activity of

the protein as it functions in the cell) cannot itself be used to distinguish between direct vs. indirect inhibitors of the POI since the claimed invention only recites "determining whether the chemical agent exerts a greater effect on the responsive change in the phenotypic characteristic of the first cell line relative to the second cell line" wherein the second cell line produces the POI at lower levels or not at all.

With regard to Hsiao et al. and Ledwith et al. not using a graded cellular response or any other responsive change in a phenotypic characteristic, the examiner reiterates the arguments made in the previous Office Actions concerning the responsive phenotypic changes evoked by the expression of the enzymes (i.e. $p21^{ras}$) in cells and that practicing the claimed method would identify agents which are not direct inhibitors (or activators) of a target enzyme such as $p21^{ras}$. Further, unidentified experimentation would be required to identify whether any given potential inhibitor or activator actually interacts directly with the POI. The claimed method, at best, can be used as a rough screen to determine whether a given agent has a phenotypic effect on cells over-expressing the POI, but any further information as to whether the agent is a direct inhibitor or activator (i.e. by direct binding) of the POI cannot be determined using the claimed invention.

With regard to the identification of tamoxifen as a direct inhibitor of PKC, while the instant method identified tamoxifen as a potential direct inhibitor of PKC, the actual identification of tamoxifen as a direct inhibitor had to await direct binding assays different from the methods recited in the instant application.

With regard to the decision of the Technical Board of Appeal of the EPO in case T 0729/00 3.3.4, it is noted that the decision was adverse to the patentee and the patent was revoked. The argument that the decision of the Opposition Division of the EPO which was the basis for the appeal was in favor of the patentee is irreverent in view of the decision on appeal. While the claims before the Technical Board of Appeal were not the same as the instant claims (basically the claims differ in that the instant claims recite methods of determining whether a agent is a **direct inhibitor or activator** of a POI while the claims before the Technical Board of Appeal did not recite "direct" inhibitors or activators, only a method of determining whether an agent was an inhibitor or activator of the POI), it is noted that the issue of whether the specification provided an enabling disclosure sufficient for the user to distinguish between direct and indirect inhibitors of the POI is relevant to the instant claims. The Technical Board of Appeal found that the user would be unable to distinguish between agents which were direct inhibitors or activators of the POI vs. agents which were acting by some other (indirect) mechanisms. Finally, while the decision is not binding on the US Patent Office, the decision is relevant to the issues at hand in the instant case.

Claims 121-128 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining, at best, whether a substance interacts in some fashion, with a POI so as to inhibit or activate said POI, does not reasonably provide enablement for determining whether a substance is a direct inhibitor of a POI. The specification does not enable any person skilled in the art

to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims read on methods of determining whether a substance is a "specific" inhibitor or activator of a POI. The CAFC has ruled that the term "specific" does not mean direct inhibitor or activator but instead reads on a method for determining whether a substance interacts directly or indirectly with the POI. The embodiments of the instant method claims which read on determining whether a substance is a direct inhibitor or activator of a POI are not enabled for the following reasons.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. I 986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

1) 1) Unpredictability of the art. The art in this area is unpredictable. In order to practice the claimed invention the skilled artisan must be able to distinguish between substances which act indirectly to inhibit or activate the target protein or enzyme of interest (POI) vs. those agents which directly interact (bind to) with the POI so as to inhibit or activate the POI. Applicant does indicate that: "Substances which specifically inhibit or inactivate

the POI may be distinguished from substances which affect cell morphology or growth by other mechanisms in that they have a greater effect on the test lines than on the control lines." (Specification, p. 5). Applicant also recites: "What we are looking for is a increase in the phenotypic change exhibited by the cell which becomes greater with increased expression of the POI. We call this a "graded response" and it is by this specialized response that we distinguish inhibitors or activators of the POI from agents that act upon other cell metabolites to affect a phenotypic change." (Specification, p. 12). However, this disclosure does not provide guidance on how the skilled artisan would distinguish between chemical agents which directly interact with the POI vs. those which affect the POI by indirect means. For example, if the skilled artisan would attempt to practice the claimed invention to identify inhibitors or activators of the human bladder c-Ha-ras oncogene (See Hsiao et al., Mol. Cell. Biol., 1986, Vol. 6, No. 6, pp. 1943-1950) and contacted cells overexpressing the c-Ha-ras oncogene as well as cells which did not express the oncogene, with compounds such as TPA or teleocidin, etc. the skilled artisan would observe a greater phenotypic effect on the test cell line compared with the control line. Given applicant's disclosure, the skilled artisan would identify TPA or teleocidin as a substance which directly interacts with c-Ha- ras and serves as an activator of c-Ha-ras. This would not be correct because TPA or teleocidin does not directly interact with c-Ha-ras but instead may function by interacting with cellular protein kinase C receptors or other cellular receptors which in turn may interact in some fashion with the c-Ha-ras oncogene product (p21). Applicant presents no teachings on how the skilled artisan would be able to distinguish between false positive

results (as discussed above) and results which would emanate from a direct interaction between the POI and test substance. Alliteratively, applicant presents no disclosure on how the skilled artisan would distinguish between false negative results from true negative results. For example, if the POI was a protein or enzyme in the nucleus and the chemical agent was a compound able to activate or inhibit the POI but was unable to enter the cell or the cell nucleus, or was chemically modified by the cell upon uptake, a false negative result would result. Indeed, the skilled artisan, in order to practice the claimed invention, would have to perform additional, undisclosed, experimentation to determine whether the substance initially identified as a inhibitor or activator actually interacts directly with the POI and serves as an a inhibitor or activator as a consequence of said direct interaction. Given the broad scope of the claims, reading on methods of inhibiting or activating any protein or enzyme expressed in any mammalian cell and given that many POIs of particular interest (i.e. receptors, oncogenes, DNA or RNA binding proteins, etc.) which are involved in cell metabolism or cell growth are components of extremely complex metabolic and physiological pathways and can be influenced by multiple factors which do not directly interact with the PO1, it must be considered that the art with regard to methods of inhibiting or activating particular enzymes or proteins in cells is unpredictable.

2) State of the art. The art in the area of developing methods of inhibiting or activating proteins or enzymes (POIs) in cells by substances that directly interact with said POIs and monitoring responsive changes in phenotypic characteristics of the cell evoked by production of the POI is poorly developed.

3) Number of working examples. Applicants present no working examples of the claimed invention wherein a method for inhibiting or activating a particular POI in a cell is accomplished by determining whether a chemical agent that directly interacts with the POI is an inhibitor of said POI. Applicants' disclosure provides no mechanism which would enable the skilled artisan to distinguish between substances which interact indirectly with POI and agents which interact directly with the POI.

4) Amount of guidance provided by applicants. As noted above, applicants provide no guidance on distinguishing a substance which directly interacts with the POI vs. an agent which interacts in some other indirect fashion with the POI. Without such a teaching, the skilled artisan would be unable to practice the instant claims.

5) Scope of the claims. The claims are extremely broad and read on methods of inhibiting or activating any protein or enzyme in a cell.

6) Nature of the invention. The invention involves a complex area in the screening art involving the identification of substances which inhibit or activate proteins or enzymes of interest in cells.

7) Level of skill in the art. The level of skill in the art is high; however, given the lack of guidance provided by applicants, given the unpredictable nature of the art with regard to attempting to identify inhibitors or activators of proteins involved in complex metabolic and biochemical pathways and given the broad scope of the claims, it must be considered that the skilled artisan would have had to have practiced essentially trial and error experimentation in order to attempt to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that the skilled artisan would need to have conducted undue and excessive experimentation in order to practice the claimed invention.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 121-124 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 31-61 of copending Application No. 11/170,465 (hereafter the '465 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims recite the same methodology for determining whether an agent is a specific inhibitor or activator of a POI. The instant independent claims differ

from the independent claims of the '465 application in that the instant claims recite determining whether a chemical agent is a specific inhibitor or activator of an enzyme in a mammalian cell while the '465 claims recite determining whether any substance is a specific inhibitor or activator of any protein in a cell. The species of "chemical agent" is obvious however, because the specification of the '465 application specifically recites chemical agents as preferred substances to test as potential inhibitors or activators. With regard to mammalian cells and enzymes being the POIs, the '465 application likewise specifically recites use of mammalian cells as host cells for testing whether agents are specific inhibitors or activators of enzymes such as protein kinase C. It is noted that dependent claims in the '465 application also recite that the POI can be an enzyme, that the cells can be mammalian cells and the phenotypic response can be a graded cellular response. The instant claims are therefore obvious over those of the '465 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

No Claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (571) 272-0767. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D., can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David Guzo
June 19, 2006

DAVID GUZO
PRIMARY EXAMINER